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A theoretical comparison of energy available for DNA damage by electromagnetic radiations and metabolic processes

Sonali Chakrabarti
S N Bose National Centre for Basic Sciences,
JD Block, Sector III, Salt Lake, Calcutta 700 091, India

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Abstract : We analyze the relation between the wavelength of electromagnetic radiations and the experimentally observed damages to the DNA caused by radiation. We show how a radiation-analog of the damage-causing ability of various metabolic processes can be made from simple energy considerations. We further show that, the genotoxic effects of glucose and fatty acid metabolism could be equivalent to those caused by soft ionizing radiations. Experiments indicate that the DNA damages caused by toxic metabolic by-products are similar to those caused by ionizing radiations. We give a theoretical explanation for these experimental results and make some predictions which are open to experimental verification

Keywords DNA damage, electromagnetic radiation, metabolic processes

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1. Introduction

Electromagnetic radiations, mainly the UV, X-rays and γ-rays are known to cause damages to the DNA which include single strand breaks (SSB), double strand breaks (DSB), dimerizations, base alterations etc., both in vitro and in vivo [1-4]. Metabolic processes are also known to cause damages to the DNA mainly by forming toxic oxidative biproducts like the free radicals [5-7].

The reactions leading to various kinds of damages to the DNA, or any other cell component for that matter, follow different biochemical pathways each involving many different enzymes each specific to a particular reaction. So, a comparison between radiative and metabolic toxicity becomes very difficult when we concern ourselves with the actual step by step biochemical processes involved in the DNA-damaging reactions.

Fax No. 091-33-334-3477, E-mail : sonali@boson.bose.res.in.

However, a comparison appears possible, when we pay attention to a fundamental factor involved, which is *energy.* A specific amount of energy is necessary for any reaction to get started even when mediated by an enzyme, and no reaction, whether life-sustaining or damaging, can go on without energy. Though the absorption of electromagnetic radiation by a cell, and a metabolic process occurring inside a cell are two entirely different phenomena, they both have an important aspect in common,– the ability to provide energy. The electromagnetic energy when absorbed by a cell, can induce damage in a cell component. The oxidation energy produced in excess of what can be stored in a cell as ATP may also induce damage by providing the activation energy for toxic chemical reactions. The amount of damage one would expect, is a direct function of the quantity of energy supplied to the system for the damage-producing reaction to occur.

In this paper, we consider a molecule of glucose as a packet of chemical energy and compare the energy made available for cell damage by glucose oxidation with that of electromagnetic radiations. Later we apply the same principle to the case of fatty acid metabolism. The theoretical results we obtain appear to be consistent with experimental observations.

2. Toxicity in electromagnetic radiations

The biologically effective radiations are divided into three classes according to their molecular activity : the ultraviolet (UV) rays, the ionizing rays, and the visible light. In the DNA, absorption of UV (wavelength mainly in the range of 254 nm) results in considerable changes in the bases, mainly dimerization, water addition, deamination *etc.* [8-9]. Ionizing radiations are those whose interaction with the biological molecules results mostly in the ionization of the cell components which are hit. Since almost 70% of a normal cell consists of water, the primary target of these rays are water molecules which get partially converted to ions and radicals, mainly, H^+, OH^-, H, OH, e^-, H_2O_2, and HO_2. These highly reactive radiation products react with other cell components including the DNA which are damaged thereby (see [1-3]). In the DNA, ionizing radiation results in SSB and DSB along with changes or destruction of bases. An SSB (G value equal to 1) or a DSB (G value equal to 0.15) can be regarded as a much more severe type of DNA damage than base alterations like deamination, dimerization *etc* (see [4]). The absorption of visible light has not been observed to produce any detectable inactivation or DNA damage.

We draw a physical picture by putting the type of DNA damage on a wavelength scale of radiation shown in Figure 1. From Einstein's equation,

$$E = h\nu = \frac{hc}{\lambda}, \tag{1}$$

(where, E = energy of one photon, ν = the frequency of radiation, c = the velocity of light, λ = the wavelength of radiation, h = Planck's constant), smaller the wavelength, the greater is the energy contained in a photon ; from Figure 1, smaller the wavelength, more severe is the type of damage caused to the DNA. Using eq. (1), the photon energy of various electromagnetic radiations can be calculated. For visible light (wavelength λ = 400 – 800 nm), the photon energy is between 1.55 eV and 3.1 eV. This energy is not sufficient to produce either any excited state in a cell DNA or an ionized state in any of the cell components.

For the UV (wavelength λ = 400 – 200 nm), the photon energy varies from 3.1 eV to 7.29 eV. This lies in the range of various excitation energies of purine and pyrimidine base structures in the DNA which are around 4.67 eV. This explains the absorption of UV by the DNA accompanied by various base alterations including the formation of purine and pyrimidine dimers. The probability of formation of an SSB or DSB with UV would be very low since the non-enzymatic breakage of a phosphodiester bond requires energy much higher than that present in one UV radiation photon.

Wavelength	Effect of Radiation	Energy
Ionizing Radiation	Double Strand Break Single Strand Break Base Change Base Damage	
λ-200 nm		6.2 eV
UV	Dimerization De-amination Other Changes in Base	
λ-400 nm		3.1 eV
Optical	No Observable Damages	
λ-800 nm		1.55 eV

Figure 1. Schematic diagram of the wavelength dependence of types of DNA damage

Ionizing radiation includes the X-rays (wavelength ~ 5×10^{-2} nm) and the γ-rays (wavelength ~ 1×10^{-4} nm) along with all other electromagnetic radiations with wavelengths below 200 nm. It is known that a system absorbs a non-ionizing radiation which includes the UV, and gets affected only when the radiation energy is equal to the excitation energy of the target molecules. If the wavelength, *i.e.* the energy does not match, the radiation would pass unabsorbed. Einstein's photo electric equation has a different prescription for ionizing radiations. Although this equation given by $K_{max} = h\nu - \phi_0$ was for determining the maximum kinetic energy of electrons knocked out from a metal by ionizing radiations, it can be easily extrapolated to encompass biological systems. Ionizing radiations with energies greater than or equal to the ionization energy of the target molecules get absorbed, and the photon energy left over after ionization remains with the ionized molecules for further reactions. So if the system is a living cell or a solution containing DNA, there are two possibilities. A photon can directly hit a DNA molecule whereby the entire photon energy gets used up causing a very serious damage, like a single or a double strand break. Secondly, and more likely, since 70% of a cell is water, the photo energy can get absorbed by the water molecules, which get ionized. And if the photon energy is in excess of that required for ionization, the ions so formed already carry the activation energy required for further reactions. This causes the high reactivity of the ions and radicals formed when a system is exposed to an ionizing radiation, and the presence of this excess energy is potentially damaging to the system as it can trigger cascades of toxic reactions within the system.

3. Toxicity in metabolism

The term *metabolism* encompasses a great number of complex biochemical reactions taking place in the living cell. Experiments indicate that metabolism can cause cell damage by producing toxic by-products like the super oxide free radical O_2^-, hydroxyl radical OH, hydrogen peroxide

H_2O_2 *etc.* which are similar to those generated by ionizing radiations [5-7, 12-14]. We start with a very important, but relatively simple metabolic reaction, which is the oxidation of glucose to water and carbon dioxide with the formation of ATP. ATP molecules, act as the storehouse of 'utilizable' energy in a cell and are essential for providing the energy to carry out the life processes. In spite of so many enzymes involved, glucose metabolism is not 100% efficient. Not all the energy released from glucose get converted to the phosphate bond energy in the ATP [10]. The unutilizable energy released within the cell has the potential to cause damage to the DNA as will be shown below. We next show that fatty acid metabolism has even greater potential for DNA damage. As we all know, glucose and fatty acid metabolisms are responsible for providing most of the energy to a living cell to carry out life processes. So it would be interesting to make a theoretical estimate of their DNA damaging potentials, if any, and compare them to known radiation damages which are both theoretically and experimentally better understood.

3.1 Glucose metabolism :

The energy from the sunlight gets trapped as chemical energy in the glucose molecules through photosynthesis given by the overall equation

$$6CO_2 + 6H_2O + 686\text{kcal} = C_6H_{12}O_6 + 6O_2.$$

Similarly, combustion of glucose in oxygen is governed by the overall reaction

$$C_6H_{12}O_6 + 6O_2 = 6CO_2 + 6H_2O + 686\text{kcal}.$$

Glucose metabolism is the biological oxidation of glucose where again the molecules are broken down to carbon dioxide and water releasing the stored chemical energy. This energy release is associated with the formation of energy-rich ATP molecules which act as the storehouse of usable energy for the cell. Study shows that aerobic oxidation of one mole of glucose in the living cell yields 38 moles of ATP. Also, 7300 calories of free energy is conserved per mole of ATP produced [10, 11].

The overall reaction can be written as [11]

$$C_6H_{12}O_6 + 6O_2 + 38ADP + 38P_i \rightarrow 6CO_2 + 6H_2O + 38ATP.$$

With 7300 calories stored per mole of ATP, 38 moles of ATP store 277.4 kcal of energy per mole of glucose. So, when one mole of glucose is metabolized in the cell to be completely broken down to CO_2 and H_2O, a total of 686 kcal of energy is released within the cell, out of which only 277.4 kcal is stored in the ATP as utilizable energy. The rest 408.6 kcal released is not stored as ATP. This excess energy within the cell would have the potential to cause damage to the DNA, if it is large enough to produce excited states (like UV) or ionized states (like ionizing radiation) in the DNA, or other molecules in the cell.

A molecule of glucose can be considered as a single packet of chemical energy. Since 408.6 kcal of unusable energy is released by the biological oxidation of a mole (6.023×10^{23} molecules) of glucose, the potentially toxic energy released from a single glucose molecule would be 67.84×10^{-23} kcal, *i.e.* 17.63 eV. This energy, even if released as heat, can provide the activation energy for the formation of oxidative free radicals responsible for metabolic toxicity. A radiation photon of wavelength 70.33 nm would release the sam mount of energy when absorbed in a biological sample.

3.2 Fatty acid metabolism :

The combustion of 1 mole of palmitic acid releases a considerable amount of energy, and the precise amount has already been determined to be 2340 kcal, and also calculations based on experiment show that oxidative breakdown of palmitic acid leads to the formation of 129 moles of ATP [10]. This means, out of 2340 kcal released, $129 \times 7.3 = 941.7$ kcal is trapped in the cell in the form of ATP, and the rest 1398.3 kcal released cannot be utilized by the cell, and has a potential to cause damage.

The excess energy released during the cellular oxidation of a single palmitic acid molecule is 232.16×10^{-23} kcal, *i.e.* 60.36 eV. The same amount of energy is released by an ionizing radiation photon of wavelength 20.53 nm. when absorbed in a cell.

4. Conclusion

There are quite a number of experimental evidences that the metabolic damages have similarities with those caused by ionizing radiations [5-7, 12-14]. Assuming, as a first approximation, the glucose molecule to be a black box containing the photosynthetic energy, we show here that the excess unutilizable energy released during a single glucose molecule metabolism is actually in the range of the energy of a soft ionizing radiation photon. Also the potentially toxic energy released in the fatty acid metabolism is greater than that of glucose metabolism. We anticipate that the long term toxic effects of metabolic processes can be more effectively studied and compared by exposing biological samples to the very soft ionizing radiations in the range ~ 10^1 nm as indicated by our theoretical findings based on energy considerations, rather than by using the high energy X-rays (~ 10^{-2} nm), γ rays (~ 10^{-4} nm) or the low energy UV (~ 254 nm) generally used in the radiation damage-repair experiments on the DNA.

While it is clear that the unutilizable energy released during metabolism is not released like a photon at a single wavelength, the observation that metabolic activity causes the damages of similar nature as that of ionizing radiations, strongly suggests that the spectrum in which the energy is released must be peaked somewhere around those wavelengths. Successful understanding of this process involves in determining cross-correlation of the spectrum at which metabolic energy is released and the probabilities of each damage causing reaction. This would be pursued in near future.

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